

Class Review with New Drug Evaluations: Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Date of Review: January 2018

Generic Name: valbenazine

Generic Name: deutetrabenazine

Generic Name: tetrabenazine

End Date of Literature Search: November 7, 2017

Brand Name (Manufacturer): Ingrezza® (Neurocrine Biosciences Inc.)

Brand Name (Manufacturer): Austedo® (Auspex Pharmaceuticals Inc.)

Brand Name (Manufacturer): Xenazine® (Valeant Pharmaceuticals Inc.)

Dossier Received: Yes - Ingrezza®; Yes - Austedo®; Yes – Xenazine®

Purpose for Class Review:

To define place in therapy for vesicular monoamine transporter 2 (VMAT2) inhibitors recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of adults with tardive dyskinesia (TD) or Huntington chorea (HC) as a result of Huntington's Disease (HD).

Research Questions:

1. Do VMAT2 inhibitors differ in efficacy when use to treat patients with TD or HC? How do VMAT2 inhibitors differ in efficacy or effectiveness from other pharmacological therapies used to manage TD or HC?
2. Do VMAT2 inhibitors differ in adverse events or tolerability when used for the treatment patients with TD and HC? How do VMAT inhibitors differ in safety or harms from other pharmacological therapies used to manage TD or HC?
3. Are there subgroups of patients with TD or HC based on demographic characteristics (i.e., age, gender, ethnicity, comorbidities, disease duration or severity) in which one VMAT2 inhibitor may be associated with reduced effectiveness or greater harm than the other VMAT2 inhibitor or other pharmacological therapies used to manage these conditions?

Conclusions:

Efficacy

- This review identified 2 new VMAT2 inhibitors, valbenazine and deutetrabenazine, 2 clinical practice guidelines (published prior to the approval of valbenazine and deutetrabenazine)^{1,2}, 3 systematic reviews³⁻⁵ and 4 randomized controlled trials⁶⁻⁹. Prior to the approval of valbenazine and deutetrabenazine, the only VMAT2 inhibitor available was tetrabenazine which is approved for the use in patients with HC and used off-label for TD. Newer VMAT2 inhibitors are indicated for TD and HC symptom management. **Table 1** lists commonly used outcomes in studies of TD and HD. Recommendations included in this review come from small, short-term studies that are primarily funded by industry. The overall quality of evidence available for consideration is considered low. There is insufficient evidence on subgroup comparisons.

Table 1. Outcome Assessment Measurements for Tardive Dyskinesia and Chorea Symptoms

Outcome	Description	Minimal Clinically Significant Change	Clinical Relevance
Tardive Dyskinesia			
Abnormal Involuntary Movement Scale (AIMS)	Validated 12-item scale with a total score ranging from 0-28. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements).	Not defined	Interpretation of scores has not been well-established and may lack sensitivity due to limited range and non-specificity for movement frequency.
Huntington's Disease			
Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS)*	Scoring ranges from 0-106 points with higher scores indicating greater disability.	Not defined	Limited evidence suggests a 1-point increase, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.
Unified Huntington's Disease Rating Scale—total chorea movement subscore (UHDRS-TCS)*	Subscore is based on frequency and severity of chorea in 7 areas of the body on a scale of 0-28, with a higher number indicating worse disease.	Not defined	Most studies show a difference of 2-4 points which represents a 7-14% change.
Tardive Dyskinesia and Huntington's Disease			
Patients' Global Impression of Change (PGIC) score	PGIC measures patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Patients' perception of symptom improvement is critical in justifying use of therapy.
Clinical Global Impression of Change (CGIC)	CGIC is a clinician perspective of the severity of the patient's symptoms using a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Limitations to this analysis is reliance on provider recall to determine symptom improvement.
Clinical Global Impression – Tardive Dyskinesia (CGI-TD)	CGI-TD is a modified version of the CGIC utilizing the same Likert scale with a focus on tardive dyskinesia symptoms.	Not defined	Limitations to this analysis is reliance on provider recall to determine symptom improvement.
Abbreviations: TD = tardive dyskinesia			

* This scoring system was designed by the Huntington Study Group which also conducted the study of deutetrabenazine for the treatment of HD.

- There is insufficient direct comparative evidence between VMAT2 inhibitors or other active treatments for TD and HD for efficacy outcomes. There is insufficient evidence for the use of VMAT2 inhibitors for treatment of dyskinesia associated with other conditions in adults (e.g., Parkinson's disease and Tourette syndrome). There is insufficient evidence to evaluate long-term efficacy or safety of VMAT2 inhibitors and long-term data in larger populations are needed to determine the significance of harms observed in short-term phase 3 trials.

Tardive Dyskinesia

- There is low quality evidence based on one phase 3, 6-week randomized, placebo-controlled trial that valbenazine is associated with statistical improvement in the AIMS score to reduce involuntary movements in patients with TD.⁶ In patients with schizophrenia, schizoaffective disorder, or mood disorder with a history of antipsychotic use, adjusted mean improvement in AIMS score was -1.9 points (95% CI, -3.0 to -0.7; p=0.002 vs. placebo) with valbenazine 40 mg daily and -3.2 points (95% CI, -4.2 to -2.0; p<0.001 vs. placebo) with valbenazine 80 mg daily, and -0.1 points with placebo.⁶ A post-hoc subgroup analysis found patients not using antipsychotic medications may have responded better than those on antipsychotic therapy.
- There is low quality evidence that the number of patients who reported overall improvement in their symptoms, defined as “improved” or “very much improved” by the PGIC, were lower with valbenazine 40 mg and valbenazine 80 mg compared to placebo (31.7%, 24.3% and 42.0%, respectively).⁶ The inferior efficacy of valbenazine versus placebo raises important concerns of the benefit versus risk of valbenazine.¹⁰
- There is low quality evidence that deutetrabenazine decreases AIMS scores in adult patients with TD based on evidence from two 12-week, randomized controlled trials.^{8,9} The first trial found deutetrabenazine 24 mg decreased AIMS scores by a mean of -1.8 points versus placebo (95% CI, -3.0 to -0.63; P=0.003) and deutetrabenazine 36 mg decreased AIMS scores by a mean of -1.9 points versus placebo (95%; -3.09 to -0.79; p=0.001).⁹ The number of patients with at least a 50% improvement in AIMS score was higher in patients treated with deutetrabenazine 24 mg (absolute risk reduction [ARR] 23%/Number-needed-to-treat [NNT] 5 over 12 weeks) and 36 mg (ARR 24%/NNT 5 over 12 weeks) compared to placebo.⁹ The second study found deutetrabenazine (mean dose 38.8 mg) decreased AIMS score by -3.0 points versus -1.6 points in patients treated with placebo (mean difference [MD] -1.4; 95% CI, -2.6 to -0.2; P=0.019).⁸
- Similar to valbenazine, there is low quality evidence that PGIC scores were not improved by deutetrabenazine compared to placebo in patients with TD based on evidence from two studies.^{8,9}
- Evidence for the use of tetrabenazine comes from a Class III study (non-randomized, controlled study) that demonstrated a 54.2% reduction in AIMS scores compared to placebo (p<0.001) and a 60.4% reduction in patient AIMS self-rating score (p<0.001). Institute for Clinical and Economic Review (ICER) report considers evidence insufficient to make a recommendation for tetrabenazine for the treatment of TD symptoms.⁴
- The Institute for Clinical and Economic Review (ICER) found the evidence for the use of valbenazine and tetrabenazine in TD to be “promising but inconclusive” and “current prices are far out of alignment with the benefits measured in clinical trials”.⁴

Huntington Chorea

- There is low quality evidence from one 12-week study that deutetrabenazine (mean dose 40 mg) improved UHDRS-TCS by -4.4 points from baseline compared to -1.9 points for placebo (MD -2.5; 95% CI, -3.7 to -1.3; p <0.001) in patients with mild to moderate functional impairment secondary to HD.⁷ This difference is unlikely to be clinically meaningful.
- There is low quality evidence from one study in patients with HD that treatment success based on PGIC scores, defined as a response of “much” or “very much” improved, was higher with deutetrabenazine (mean dose of 40 mg) compared to placebo (deutetrabenazine 51% versus placebo 20%; ARR 31%; NNT 4 over 12 weeks).⁷

- There is low quality evidence, based on one study of 84 patients, that tetrabenazine 100mg improves UHDRS-TCS when compared to placebo (MD -3.5 points; 95% CI, -5.2 to -1.9; p<0.0001).⁵ One small study of short duration limits strong conclusions of meaningful clinical improvement.

Safety

- Patients with an uncontrolled depression or at high risk of suicide were excluded from deutetrabenazine and tetrabenazine trials because of increased risk of depression and suicidality associated with their use.^{11,12} FDA has issued black box warnings for deutetrabenazine and tetrabenazine against the use of these treatments in patients with a history of depression or prior suicide attempts. Valbenazine does not carry this warning; however, patients with any unstable psychiatric condition were excluded so the impact of its use in this population is unknown.
- All VMAT2 inhibitors may increase the QT interval.¹¹⁻¹³ Use of VMAT2 inhibitors should be avoided in patients with congenital long QT syndromes or with arrhythmias associated with prolonged QT interval. This risk may increase when VMAT2 inhibitors are used in general clinical practice and there is increased potential to be used concomitantly with other drugs (e.g., antipsychotics) that increase the QT interval.
- Common adverse effects for VMAT2 inhibitors is somnolence and dry mouth. Akathisia occurred in 3.3% of patients on valbenazine versus 1.3% on placebo. Deutetrabenazine was associated with increased incidence of diarrhea. Both deutetrabenazine and tetrabenazine were associated with higher rates of fatigue than placebo.

Recommendations:

- Create a new PDL class for VMAT2 inhibitors.
- Implement prior authorization (PA) criteria for valbenazine, deutetrabenazine and tetrabenazine to ensure appropriate use (see Appendix 3).
- Determine PDL status after evaluation of drug prices in the executive session.

Background:

Tardive Dyskinesia

Tardive dyskinesia is a delayed-onset involuntary movement disorder which commonly occurs in patients treated with chronic dopamine receptor blocking agents (DRBA). DRBAs are commonly prescribed for a wide range of psychiatric conditions (e.g., second-generation antipsychotics) or certain gastrointestinal disorders (e.g., metoclopramide).¹⁴ While TD typically manifests after 1-2 years of routine exposure to DRBAs, it may occur within months of starting treatment. The yearly rate of TD development in patients treated with DRBAs is approximately 2-5% with a cumulative 5-year incidence of approximately 20% to 25%.² It is estimated that 20-50% of patients treated with a DRBA ultimately develop TD.^{14,15} Neuroleptic-induced TD is higher in women, especially those middle-aged and elderly, where incidence rates may reach as much as 30% after 1 year of cumulative exposure.¹⁴ TD may persist for years even after discontinuation of the DRBA, and in many cases, may not be reversible.¹⁶ The debilitating effects of TD lead to increased mortality, decreased physical functioning, medication nonadherence, and a lower quality of life.¹⁷

TD is one of many disorders thought to arise from dopamine receptor blockade, but it is distinct from other movement disorders such as Parkinson's disease, Tourette syndrome, and Huntington's disease.¹⁴ Genetic testing, neuroimaging, and other diagnostic work-ups may be necessary to rule out other causes of dyskinesia.¹⁴ The Diagnostic and Statistical Manual of Mental Disorders definition for DRBA-induced TD requires exposure for a DRBA for at least 3 months (or 1 month in patients $\geq$ 60 years of age), presentation of symptoms within 4 weeks after withdrawal of an oral medication (or within 8 weeks of a depot medication), and persistence of symptoms for 1 month after discontinuation of offending agent.¹⁴ Irregular, repetitive, orofacial movements including lip smacking, jaw clenching, facial grimacing, and tongue protrusions are classic symptoms of TD that range in severity from mild annoyance to impairment of

speech and swallowing.¹⁶ TD patients may commonly experience random jerking movements in their upper extremities, lower extremities, and trunk which may interfere with daily living activities and create challenges for caregivers.¹⁸

Many explanations circulate regarding the pathophysiological link between DRBA use and TD. Chronic DRBA exposure, notably first generation antipsychotics, may cause upregulation and hypersensitization of post-synaptic dopaminergic (D2) receptors which disrupt normal dopamine recycling, most notably in the nigrostriatal pathway.¹⁹ Early removal of D2 receptor blockade may slowly reverse the dyskinesia, but the cumulative effects of long-term use of DRBAs may result in irreversible TD.¹⁴ Increased dosages of neuroleptic agents have demonstrated temporary improvements of TD symptoms which lends credibility to the dopamine receptor upregulation hypothesis.¹⁹ Other possible explanations under investigation include cholinergic deficit, gamma-aminobutyric acid (GABA) depletion or abnormalities of striatal GABA neurons, neurotoxicity, and oxidative stress.^{14,15,19}

There is currently no curative treatment for TD, and limited evidence is available to guide its management.¹ Estimated remission rates for TD vary from as little as 1% up to 62%.¹⁶ TD occurs in roughly one-third of patients treated with first generation antipsychotics as compared to 13% on second generation (atypical) agents.^{17,19} Three broad approaches have been used to manage TD including antipsychotic dose reduction, switching antipsychotic drug therapy, or addition of adjunctive agents.³ Pharmacologic options for adjunctive treatment of TD are limited. Off-label use of tetrabenazine, clonazepam, amantadine, levetiracetam, resveratrol, and even ginkgo biloba have been used for TD symptom management with varying levels of success.¹⁹ Other studies have investigated off-label use of medications for TD treatment, but authors concluded that prudent use and monitoring of atypical antipsychotics is key to management of TD symptoms.¹⁹ For cases of TD resistant to drug therapy, non-systemic options such as deep brain stimulation have been reported to provide some benefit.¹⁹

The assessment of TD is challenging due to the variability in research criteria and different rating scales.²⁰ The AIMS is a clinical tool frequently used for early detection and surveillance of TD.³ The AIMS has 12 items which assess 7 commonly affected anatomical locations with a total score ranging from 0-28. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from 0 (no abnormalities) to 4 (severe movements).³ The full assessment tool also contains an overall judgement of 3 abnormal movements also rated on a scale from 0-4, and 2 yes/no items concerning problems with teeth and dentures.¹³ The AIMS can be completed in less than 10 minutes, and evaluation is suggested at least every 6 months for those on typical antipsychotics.³ However, there is not a well-established guideline for interpretation of AIMS scores, and there is criticism that it lacks sensitivity due to its limited range and non-specificity for movement frequency.³ Each section of the AIMS may be totaled, but overall scores are generally not reported. There is no MCID established and evidence has not demonstrated that improvement in AIMS score translates into improved function or quality of life for patients.¹⁰

Huntington's Disease

Huntington's disease results from a gene abnormality of an exon 1 CAG (cytosine-adenine-guanine [amino acid sequence]) trinucleotide expansion in the huntingtin (HTT) gene. Huntington Disease is a progressive, hereditary neurodegenerative disease that results in involuntary movements, cognitive dysfunction and psychiatric symptoms. Early stages of HD is often characterized by deficiencies in voluntary motor function while mid stages are associated with more of an impact on motor coordination and function.²¹ Optimization of quality of life is the focus of HD treatment through symptom management since there is no cure or disease-modifying therapies. The estimated incidence of HD is 5 in 100,000 people in the US.²²

Prior to the approval of deutetrabenazine, the only treatment approved for chorea symptoms associated with HD was tetrabenazine. The use of tetrabenazine is limited by variable CYP2D6 metabolism that often results in a 3-times daily dosing frequency.¹¹ Tolerability is also an issue with tetrabenazine with common

adverse effects such as sedation, fatigue, akathisia, anxiety and nausea. Olanzapine, risperidone, aripiprazole, clozapine, haloperidol and fluphenazine have also been used as off-label treatment options for patients with HC.²

The severity of HC and functional impact is measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and is the main endpoint used in many trials. The UHDRS-TMS motor scale uses 106 questions to measure chorea, parkinsonism, dystonia, eye movements, and other signs. There are 31 items that are graded 0 (not affected) to 4 (most severely affected).² There is limited evidence that a 1-point increase in the UHDRS-TMS, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children. In studies of patients with a diagnosis of HD, the mean annual change in patients UHDRS-TMS was 3.8 points. AAN guidelines define the change in subscores of less than 1-point decrease in UHDRS as unimportant, 1 to less than 2-point decrease as modestly important, 2 to less than 3-point decrease as moderately important and more than a 3-point decrease as very important.²

The UHDRS total chorea score (UHDRS-TCS) is a subscore which rates facial, bucco-oral-lingual, trunk and extremity chorea. Standardized assessment of chorea based on the UHDRS-TCS subscore is determined by frequency and severity of chorea in 7 areas of the body by a scale of 0-28, with a higher number indicating worse disease.² This subscore represents 23% of the overall UHDRS-TMS and is recommended for determining the impact of chorea symptoms over using the UHDRS-TMS.²¹ The clinically important change for this endpoint has not been determined.

Symptom Assessment Used for Both Tardive Dyskinesia and Huntington's Disease

The PGIC is used to determine the patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse". The CGIC is a clinician perspective of the severity of the patient's symptoms utilizing the same scale as the PGIC.⁴ Limitations to the CGIC is the reliance on provider recall of patient symptoms. The CGI-TD score is used to rate the overall change in tardive dyskinesia symptoms on a scale from 1 ("very much improved") to 7 ("very much worse"). Since there are no curative treatments for TD or HD, outcomes related to improvement in symptoms are very important and should be a major consideration in treatment selection. The SF-36 quality of life assessment is also used with a higher score indicating an improved quality of life.

The FDA recently approved valbenazine, a selective, reversible VMAT2 inhibitor, for the treatment of adults with TD.^{12,13} Deutetrabenazine, a VMAT2 inhibitor initially approved for HC, also recently received FDA approval for TD treatment. A third agent, tetrabenazine was approved in 2008 for use to treat symptoms of HC and has been used off-label for severe TD; however, mixed efficacy and numerous safety concerns has limited its widespread use.¹¹ This document examines the efficacy and safety for the use of VMAT2 inhibitors in TD and HC.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. VMAT2 Inhibitors Indications and Dosing

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Valbenazine ¹³ (Neurocrine Biosciences, Inc.)	Tardive dyskinesia in adults	40 mg and 80 mg capsules	Initiate dose at 40 mg daily and increase to 80 mg daily after one week

Deutetrabenazine ¹² (Teva Pharmaceuticals USA, Inc.)	Chorea associated with Huntington's disease and tardive dyskinesia in adults	6 mg, 9 mg and 12 mg tablets	Huntington's disease: initiate at 6 mg/day and increase by 6 mg per day to recommended dose of 6-48 mg/day Tardive dyskinesia: initiate at 12 mg/day and increase by 6 mg per day to a recommended dose of 6-48 mg/day Doses of 12 mg or more should be given in 2 divided doses
Tetrabenazine ¹¹ (Prestwick Pharmaceuticals)	Chorea associated with Huntington's disease in adults	12.5 mg and 25 mg tablets	Initiate dose at 12.5 mg and titrate as needed to up to 100 mg daily. Doses above 50 mg daily should be divided into 3 times daily regimen

Utilization data:

While utilization for VMAT2 inhibitors is low the annual costs are estimated to be around \$75,000 or more per patient per year. There are Oregon Health Plan (OHP) fee-for-service (FFS) claims for tetrabenazine.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER) and the Canadian Agency for Drugs and Technologies² in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Tardive Dyskinesia

The National Institute of Health and Care Excellence (NICE): Interventions for Treating or Preventing Antipsychotic-induced Tardive Dyskinesia

A 2017 systematic review and meta-analysis was performed by NICE to assess the efficacy and safety of interventions to treat TD in adults.³ Randomized trials and observational studies of adults taking a stable dose of antipsychotic drugs for 3 months or more were included. The search ended prior to the approval of valbenazine and deutetrabenazine. One hundred twelve studies were identified but most trials had a high overall risk of bias. Studies were small with 8-170 participants, with the exception of some vitamin E studies which enrolled up to 264 patients.³ Interventions studied to manage TD symptoms included dose adjustment of antipsychotics, switching antipsychotics and addition of pharmacotherapy to antipsychotics.

Evidence from two small studies of very low quality found reduction of the antipsychotic dose did not result in clinically important improvement relative to continuing the antipsychotic (risk ratio [RR] 0.42; 95% CI, 0.17 to 1.04; p=0.06).³ Two studies evaluated the effect of switching antipsychotics on TD symptoms

but the results could not be combined. The first study found switching to risperidone resulted in fewer patients with no clinically important improvement in TD symptoms compared to antipsychotic withdrawal (RR of 0.45; 95% CI, 0.23 to 0.89; $p=0.02$; ARR 38%/NNT 3). Low quality evidence from a second study in 45 patients found no difference in clinically important improvement in TD symptoms when switching to quetiapine versus haloperidol (RR of 0.80; 95% CI, 0.52 to 1.22; $p=0.30$).³ Evidence from observational studies found no clear evidence of improvement in TD symptoms with antipsychotic discontinuation versus dose modification based on very low quality evidence. Two studies that evaluated the effect of benzodiazepines on TD symptoms provided very low-quality evidence of no benefit (RR 1.12; 95% CI, 0.6 to 2.09). Vitamin E was evaluated in 6 studies with similar results of no benefit (RR 0.95; 95% CI, 0.89 to 1.01) based on low quality evidence. Another low-quality study ($n=42$) found improvement in TD symptoms with use of buspirone, added to antipsychotic treatment, (RR 0.53; 95% CI, 0.33 to 0.84; $p=0.007$; ARR 42%/NNT 3). A study of very low quality could not find a difference at 18 weeks between haloperidol and tetrabenazine in the number of patients with no improvement in TD symptoms (RR 1.07; 95% CI, 0.51 to 2.23; $p=0.35$).³ Another small study found less patients on clonazepam had no clinically important improvement in TD symptoms compared to phenobarbital (40% vs. 91%, respectively).

To summarize, the only two strategies found to decrease TD symptoms were switching to risperidone (versus antipsychotic withdrawal) and adding buspirone adjunctively to the antipsychotic. All other comparisons were not clinically or numerically significant.

Institute for Clinical and Economic Review (ICER): Effectiveness and Value of Vesicular Monoamine Transport 2 Inhibitors for Tardive Dyskinesia

A 2017 review on the role of VMAT2 inhibitors in TD was produced by ICER.⁴ The focus of the review was on valbenazine, deutetrabenazine and tetrabenazine use in adults with TD. Key intermediate outcomes were AIMS, CGIC and PGIC. Eleven studies of at least 10 patients were included. Thirteen references of conference abstracts/posters were also included.⁴ Evidence identified for valbenazine and deutetrabenazine were found to be of fair to high quality studies. Evidence for tetrabenazine was determined to be of poor quality and therefore these studies were not considered in qualitative or quantitative assessments of VMAT2 inhibitors.

ICER rated both valbenazine and deutetrabenazine for the treatment of TD as “promising but inconclusive” based on improvement in AIMS scores compared to placebo but lack consistent improvement in CGIC and PGIC scores.⁴ ICER concluded that clinician and patient impressions of symptom improvement is of critical importance since the drugs were approved for this indication. ICER was also concerned with lack of long-term safety data that could reveal additional adverse events with both treatments. Deutetrabenazine carries a FDA boxed warning for depression and suicidality. Evidence for use of tetrabenazine for the treatment TD symptoms suggest a possible benefit but was rated as insufficient.⁴ Clinical trial safety data of tetrabenazine found tolerability issues from somnolence, insomnia, and depression.

Huntington’s Disease

Cochrane Collaboration – Therapeutic Interventions for Symptomatic Treatment in Huntington’s Disease

The pharmacological treatment options for the treatment of HD was reviewed.⁵ Evidence for deutetrabenazine and valbenazine was not available as they were approved after the publication date. Randomized, double-blind, placebo-controlled studies with at least 10 patients met inclusion criteria. Twenty-two studies were identified. Mean patient age was 48 years with a mean disease duration of 6.3 years. Only one trial ($n=84$) for VMAT2 inhibitors was identified, which compared tetrabenazine to placebo. Patients with a confirmatory diagnosis or a compatible family history of HD were included.

The study found tetrabenazine 100 mg daily lowered the UHDRS-TCS score by 5.0 points compared to a decrease of 1.5 points for placebo (MD 3.5 points; 95% CI, -5.2 to -1.9; $p<0.0001$).⁵ Tetrabenazine resulted in a statistically significant difference in change in CGIC score versus placebo (3.0 points vs. 3.7 points, respectively; MD 0.7 points; CI not reported; $p<0.007$); however, the clinical significance of a 0.7 point change is unlikely to be impactful to the patient. The

exploratory functional endpoints of UHDRS Functional Checklist and the 17-item Hamilton Depression scale were statistically worse with tetrabenazine compared to placebo. Five (9.2%) of patients in the tetrabenazine group discontinued treatment due to adverse events compared to none in the placebo group.⁵

Other treatments have been studied for the reduction of symptoms with HD. Use of riluzole is limited by an excess of hepatic toxicity when used at the effective dose of 200 mg daily. A study of riluzole 100 mg daily showed lack of efficacy. Two small trials studied amantadine for symptoms of chorea with HD. Pooled analysis found no difference between amantadine and placebo (MD -0.25; 95% CI, -0.93 to 0.43; p=0.10); however, a higher number of patients reported subjective improvement in symptoms and quality of life with the use of amantadine.⁵

Therapies studied which demonstrated no measurable effect on chorea symptoms of HD were: cannabidiol, clozapine, creatine, ethyl-eicosapentaenoic acid, fluoxetine, ketamine, L-acetyl carnitine, minocycline, piracetam, remacemide, sulpiride, tiapride, trans-dihydrolisuride and unsaturated fatty acids.⁵

Guidelines:

American Academy of Neurology (AAN): Treatment of Tardive Syndromes

A clinical practice guideline on the management of tardive syndromes was published in 2013 by the AAN.¹ Evidence was systematically reviewed and graded using a modified GRADE process for evidence synthesis. One of the guideline authors had substantial ties to industry. Treatments included in the guideline were anticholinergics, benzodiazepines, beta-blockers, calcium channel blockers, GABAergic compounds, neuroleptic medications, non-neuroleptic medications that affect the dopamine and noradrenaline systems, vitamin B6 and vitamin E. Each study was graded on quality of evidence, from Class I (randomized clinical trial) to Class IV (consensus/expert opinion). Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting).

There was insufficient evidence to support treatment of TD symptoms by withdrawing the DRBA (Level U).¹ Evidence was conflicting whether switching from typical antipsychotics to atypical antipsychotics reduced TD symptoms (Level U). There was insufficient evidence to support treatment of TD with acetazolamide and thiamine (Level U). Amantadine may be an option for the short-term treatment of TD (Level C). However, neuroleptics may cause TD and mask symptoms and are not recommended to treat symptoms of TD (Level U).¹ Caution should be taken if risperidone or olanzapine are used to treat symptoms of TD. The use of tetrabenazine may be considered for the treatment of TD symptoms based on evidence from two Class III studies (Level C). Clonazepam may be effective for short-term (approximately 3 months) treatment of TD and should be considered (Level B).

There was insufficient data to recommend reserpine, alpha-methyldopa, levetiracetam or anticholinergics for TD (Level U).¹ There was insufficient evidence to support use of thiopropazate, molindone, sulpiride, fluperlapine, flupenthixol, bromocriptine, nifedipine, buspirone, botulinum toxin or baclofen for treatment of TD symptoms (Level U). Galantamine is likely ineffective for the treatment of TD symptoms and is not recommended (Level C). There was insufficient evidence to determine if discontinuing biperiden is effective in treating symptoms of TD (Level U).

American Academy of Neurology (AAN): Pharmacologic Treatment of Chorea in Huntington Disease

The AAN published a treatment guideline of the management of chorea in patients with HD in 2012.² Each study was systematically reviewed and graded using a modified GRADE process for evidence synthesis. Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting). AAN guidelines are funded by the academy and authors of this guideline had received grants from industry. Dopamine-modifying drugs, glutamatergic-modifying drugs, energy metabolites, donepezil, coenzyme Q10, minocycline, and nabilone were included. Guidelines were developed before the approval of valbenazine and deutetrabenazine so guidance on these treatments are not available.

AAN guidelines recommend tetrabenazine up to 100 mg daily for patients needing treatment for HC based on level B evidence.² Two studies, graded as Class I and Class II, were used as evidence to support the recommendation. A 12-week RCT comparing tetrabenazine to placebo (n=84) found a UHDRS total maximal chorea score decrease of -5.0 points compared to -1.5 points in the placebo group (p=0.0001). CGIC scores also improved with tetrabenazine by an adjusted effect size of -0.7 units (95% CI, -1.3 to -0.2) compared to placebo. A 10% change in symptoms is unlikely to be clinically significant. PGIC scores were not reported. A second study was a tetrabenazine withdrawal study which found that patients in the early discontinuation group had a 5.3-point increase in UHDRS chorea score compared to patients continuing therapy.² Reviewers felt that tetrabenazine was likely effective in decreasing chorea symptoms but should be used cautiously as it can worsen depression and Parkinsonian symptoms often present in HD.

Amantadine 300-400 mg daily and riluzole 200 mg daily were also recommended based on Level B evidence. Short-term use of nabilone can also be considered (Level C).

Randomized Controlled Trials:

A total of 41 citations were manually reviewed from the initial literature search. After further review, 37 citations were excluded because of wrong study design (e.g., observational) or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the new drug evaluation tables below.

VALBENZAZINE NEW DRUG EVALUATION:

Clinical Efficacy:

The efficacy of valbenazine in the treatment of TD was established primarily on the basis of one 6-week randomized, parallel-group, fixed-dose, placebo-controlled study (see **Table 2**).⁶ Valbenazine 40 mg daily (n=76) and valbenazine 80 mg daily (n=70) were compared to placebo (n=79) in medically stable patients with moderate to severe TD from various centers in the US (59 sites), Canada (2 sites), and Puerto Rico (2 sites).⁶ A majority of patients were diagnosed with schizophrenia or schizoaffective disorder (66.1%) or mood disorder (33.9%) and had a DSM diagnosis of DRBA-induced TD for at least 3 months. Seventeen percent of patients were taking first-generation antipsychotic (FGA) and 77% were taking a second-generation antipsychotic (SGA). The mean baseline AIMS dyskinesia score was 10 and patients had an average 7-year history of TD. Patients with severe psychiatric disease, as indicated by a Positive and Negative Syndrome Scale (PANSS) score of 70 or more or a score of at least 50 on the Brief Psychiatric Rating Scale (BPRS), or significant unstable comorbidities were excluded. Specifically, patients with any other movement disorder more prominent than TD, such as parkinsonism, akathisia or truncal dystonia, were not included. The primary endpoint was a mean change in the AIMS dyskinesia score for items 1-7 on AIMS (range 0-28) from baseline to week 6.⁶ Global severity (questions 8-10) and problems with teeth or dentures (questions 11-12) were not assessed. The key secondary endpoint was the change in the 7-point CGI-TD score (range 1-7) from baseline to week 6.⁶ PGIC was also a secondary endpoint with scores of 1 (very much improved) or 2 (much improved) classified as PGIC “responders”.

The mean total AIMS dyskinesia score was reduced by 1.9 points in the 40 mg group and 3.2 points in the 80 mg valbenazine group, which were statistically significant differences versus the 0.1-point reduction with placebo.⁶ However, these differences are unlikely to be meaningful, especially in patients with less severe TD symptoms. A reduction in AIMS dyskinesia score of greater than 50% at 6 weeks from baseline occurred in 23.8% of patients on valbenazine 40 mg (p=0.02 vs. placebo, NNT = 7) and 40% of patients on valbenazine 80 mg (p<0.001 vs. placebo, NNT = 4).⁶ No statistically significant difference was found in CGIC scores between the valbenazine arms and placebo at week 6. The number of treatment responders, as assessed by the PGIC, in the valbenazine 40 mg group was 31.7%, versus 24.3% in the valbenazine 80 mg group and 42.0% for the placebo group.¹⁰ Patients on placebo experienced a statistically greater impression of improvement than patients on valbenazine 80 mg per day.¹⁰

There insufficient evidence to support the assertion that a statistically significant reduction in AIMS dyskinesia score is associated with clinical relevance because there is no established MCID. Additionally, PGIC scores were lower with valbenazine than with placebo which suggest that patients felt their symptoms were improved less than placebo with treatment. It is also unknown if valbenazine had different effects within the 3 types of psychiatric disorders represented in the study. In addition, not all patients were on an antipsychotic, and there was evidence to suggest that patients not on an antipsychotic may have responded better than patients on antipsychotic therapy.⁶ Patients with severe depression or suicidal ideation were excluded from the study so the effects of valbenazine in this population is unknown. The trial's extensive exclusion criteria limit the applicability of the data to healthy, stable psychiatric patients with few to no comorbidities. The effect of valbenazine in complex patients, prescribed multiple high-dose antipsychotics or patients with other types of DRBA-induced TD is unknown. It was unclear why patients were not assessed using the global judgement portion of the AIMS tool. Given the short study duration, unestablished MCID for the AIMS tool, and lack of clinician-reported and patient-reported impression of improvement, the clinical value and long-term effectiveness of valbenazine is unclear.

Clinical Safety:

In KINECT 3, 5.3% of patients in the placebo group and 6% of patients in the valbenazine group prematurely discontinued their medication due to an adverse event.⁶ Serious adverse events were reported more frequently in the valbenazine group than placebo (6.6% vs. 3.9%, respectively). However, the specific types of adverse events leading to early discontinuation of treatment or types of serious adverse events were not reported in the study. The most common adverse effects for valbenazine versus placebo were somnolence (5.3% vs. 3.9%, respectively), dry mouth (3.3% vs. 1.3%, respectively), and akathisia (3.3% vs. 1.3%, respectively).¹³ Pooled safety data from 3 controlled studies (n=445) reported that somnolence was present in 11% of valbenazine subjects versus 4% for placebo which was higher than what was found in KINECT 3.⁶ The short study duration limits the ability to draw conclusions on the safety of valbenazine.

The FDA safety analysis noted QT prolongation with valbenazine which prompted addition of this warning to the labeling.⁶ Due to potential increases in serum concentrations of valbenazine's active metabolite ([+]- α -dihydrotetrabenazine), labeling also includes recommendations to avoid concomitant use with monoamine oxidase inhibitors (MAOI) and strong CYP3A4 inducers and to reduce valbenazine dose with co-administration of strong CYP3A4 and CYP2D6 inhibitors.¹⁴ Valbenazine is not recommended for patients with severe renal impairment.¹³

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Functional improvement
- 2) Symptom improvement
- 3) Health-related quality of life
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) AIMS dyskinesia total (change from baseline)

Table 3. Valbenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Hauser et al. ^{6,10,13} DB, PC, Phase 3, RCT	1. valbenazine 40 mg daily 2. valbenazine 80 mg daily 3. Placebo 6 weeks	<u>Demographics:</u> -Mean age: 56 years -Age ≥65 years: 16% -Male: 54% -White: 56% -Black: 38% -Mean AIMS dyskinesia score (items 1-7): 1. 9.8 2. 10.4 3. 9.9 -Schizophrenia/ schizoaffective: 66% -Mood disorder: 34% -APD: 85.5% -SGA: 77% -Antidepressant: 66.5% <u>Key Inclusion Criteria:</u> -Age: 18-85 -Diagnosis of schizophrenia or schizoaffective disorder or mood disorder per DSM-IV criteria for ≥ 3 mo. -DSM diagnosis of DRBA-induced TD for ≥ 3 mo. -Moderate to severe TD per external centralized AIMS video rating score -Maintenance meds at a stable dose for ≥30 days before screening <u>Key Exclusion Criteria:</u> -NCYP3A4 inducers, dopamine agonists, MAOIs -PANSS total score ≥70 or CDSS total score ≥10 -Unstable mental conditions -h/o suicidal ideation -h/o prolonged QT	<u>ITT:</u> 1. 70 2. 79 3. 76 <u>PP:</u> 1. 52 2. 61 3. 66 <u>Attrition:</u> 1. 17% 2. 11% 3. 9%	<u>Primary Endpoint:</u> Change total AIMS score at Week 6: 1. -1.9 2. -3.2 3. -0.1 1. VBZ 40 mg vs. PBO -1.8 (95% CI, -3.0 to -0.7) p= 0.0021 2. VBZ 80 mg vs. PBO -3.1 (95% CI, -4.2 to -2.0) p <0.0001 <u>Secondary Endpoints:</u> % w/ ≥50% decrease in AIMS score: 1. 24% 2. 40% 3. 9% 1. VBZ 40 mg vs. PBO 15% (95% CI NR; p= 0.02) 2. VBZ 80 mg vs. PBO 40% (95% CI NR; p<0.001) LS Mean CGI-TD at Week 6: 1. 2.9; p=NS vs. PBO 2. 2.9; p=NS vs. PBO 3. 3.2 PGIC Treatment Responders 1. 31.7% 2. 24.3% 3. 42.0%	NA NA 15%/7 31%/4 NS NS	SAE 1. 5.6% 2. 7.6% 3. 3.9% DC due to AE: 1. 5.6% 2. 6.3% 3. 5.3% <u>TEAEs:</u> Somnolence 1. 5.6% 2. 5.1% 3. 3.9% Akathisia 1. 4.2% 2. 2.5% 3. 1.3% Dry mouth 1. 6.9% 2. 0% 3. 1.3% p-values NR	NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> LOW. IWRS used to randomly assign participants. Use of APDs differed between groups. Ultra-rapid and poor CYP2D6 metabolizers also differed but implications of these differences are unclear. <u>Performance Bias:</u> LOW. Participants, investigators, study site personnel, central AIMS video raters, and the study sponsor blind to treatment assignment. <u>Detection Bias:</u> LOW. AIMS examination video reviewed/scored by blinded experts via central AIMS video. Video rater pairs provided consensus scoring. <u>Attrition Bias:</u> UNCLEAR. Attrition higher in treatment groups (14% vs. 9%). Not a true ITT as analysis excluded some randomized patients. Analyses conducted in the per-protocol population considered supportive. <u>Reporting Bias:</u> UNCLEAR. Study funded by drug sponsor. Of 9 authors, 4 directly employed by drug sponsor and 4 others served as consultants and/or received honoraria from sponsor. Sponsor provided support for writing and editorial assistance of the manuscript. Three authors have equity in drug sponsor. Critical review of manuscript drafts provided by full-time employee of drug sponsor. Applicability: <u>Patient:</u> Narrow inclusion criteria limits applicability to patients with schizophrenia, schizoaffective disorder, or mood disorder w/ DRBA-induced TD; study excluded high-risk or medically unstable, violent or suicidal patients; concomitant psychiatric medications likely representative of target population but highly variable. <u>Intervention:</u> VBZ doses used approved by FDA. <u>Comparator:</u> PBO appropriate to assess efficacy. <u>Outcomes:</u> AIMS test score change from baseline, but MCID is unclear; AIMS score results highly subjective and not linear; PGIC and CGIC more clinically relevant outcomes but these did not support efficacy of VBZ. <u>Setting:</u> 63 centers in North America (59 in the United States, two in Canada, and two in Puerto Rico).

Abbreviations: AIMS = Abnormal involuntary movement scale; ARR = absolute risk reduction; APD = antipsychotic drug; CDSS = Calgary Depression Scale for Schizophrenia; CFB = change from baseline; CGIC = Clinical Global Impression of Change; CI = confidence interval; DRBA = dopamine receptor blocking agents; ITT = intention to treat; IWRS = Interactive web response system; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MAOIs = monoamine oxidase inhibitors; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NMS = neuroleptic malignant syndrome; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PP = per protocol; Positive and Negative Syndrome Scale = PANSS; SAS = Simpson-Angus Scale; TD = tardive dyskinesia; VBZ = valbenazine; VMAT2 = vesicular monoamine transporter 2; YMRS = Young Mania Rating Scale

DEUTETRABENAZINE NEW DRUG EVALUATION:

Clinical Efficacy:

Deutetrabenazine is a VMAT2 inhibitor approved for chorea associated with HD and TD in adult patients.¹² Deutetrabenazine is a chemically modified form of tetrabenazine that has a longer half-life and lower peak concentrations levels. Deutetrabenazine has been studied in one trial for HD and two trials for TD (**Table 4**). Deutetrabenazine received an orphan drug designation for Tourette syndrome in the pediatric population.¹²

Huntington Chorea

Approval for the use in HC was based on a randomized, placebo-controlled, double-blind, multicenter study in 90 patients with HD.⁷ Deutetrabenazine was compared to placebo over 12 weeks. Inclusion criteria included a baseline UHDRS total maximal chorea score of 8 or higher (range 0-28 with lower scores indicating less chorea) and a UHDRS total functional capacity score of 5 or higher which correlates to mild to moderate functional impairment. Patients had a HD diagnosis for approximately 15 years. The mean patient age was 54 years and 56% were male. Mean UHDRS- TCS was 12.7 at baseline. Exclusion criteria included the following: uncontrolled depression as measured by a Hospital Anxiety and Depression Scale (HADS) score of 11 or more, history of significant suicidal thoughts or behavior, prolonged QT interval, hepatic or renal impairment, Unified Parkinson Disease Rating Scale (UPDRS) speech item with scores of 3 or higher, and patients with score of 11 or higher on the Swallowing Disturbance Questionnaire.⁷ Patients taking antipsychotics and dopamine agonists were also excluded. The primary endpoint was change in UHDRS-TCS from baseline (average of values from the screening period and day 0 visits) to maintenance therapy (the average of values between Week 9 and Week 12). Studies have used a change of 2.7 points in UHDRS-TCS to indicate a clinically relevant treatment difference, but this only represents a 10% change. MCID for UHDRS-TCS has not been established. Secondary endpoints of interest were the PGIC and CGIC. The PGIC and CGIC were defined as treatment success if patient response was “much” or “very much” improved at week 12.

TCS decreased by -4.4 points the deutetrabenazine group versus -1.9 points in the placebo group (MD -2.5; 95% CI, -3.7 to -1.3; P<0.001) at 12 weeks.⁷ Treatment success based on PGIC was achieved in 23 patients (51%) treated with deutetrabenazine compared to 9 patients (20%) on placebo at 12 weeks (MD 31%; 95% CI, 12.4 to - 49.8%; NNT 4). Nineteen patients (42%) in the deutetrabenazine group experienced treatment success at Week 12, based on the CGIC scale, compared to 6 patients (13%) in the placebo group (MD 29%; 95% CI, 11.4 to 46.4%; p=0.02; NNT 4). Patient satisfaction scores improved 0.7 points with deutetrabenazine compared to -3.6 points with placebo (p=0.03) based on the SF-36 validated patient satisfaction tool. After washout at week 13, total maximum chorea scores returned to baseline values.

Study limitations included extensive exclusion criteria limiting the applicability, especially in patients taking antipsychotics. The patients in this trial had worse motor symptoms at baseline compared to evidence for tetrabenazine, which make efficacy comparisons difficult.⁵ Secondary endpoints had wide confidence intervals which suggest that no treatment difference could still exist between deutetrabenazine and placebo. This is particularly important because these endpoints evaluate the patient’s perception of improvement, which is an important factor for therapies designed for symptom management.¹² Depression,

stigma and suicide rates are high in patients with HD. The study was not designed or powered to assess CGIC and PGIC so it is difficult to determine the effect of deutetrabenazine on these endpoints in such a small, short-term study.

Tardive Dyskinesia

The 2 multi-center, parallel design, placebo-controlled, double-blind, 12-week studies used to assess deutetrabenazine in management of TD symptoms were similar.^{8,9} Both studies enrolled adult patients ages 18-80 years with an AIMS score (on items 1-7) of at least 6 and stable psychiatric illness with use of DRBA for at least 3 months (or age of 60 years or older with use of DRBA for at least one month). The primary endpoint was change in AIMS score from baseline. Secondary endpoints were the number of patients experiencing treatment success based on AIMS score improvement of at least 50%, CGIC “responders” (CGIC score of “much” or “very much” improved), and PGIC “responders” (PGIC score of “much” or “very much” improved). Patient satisfaction was measured by the modified Craniocervical Dystonia Questionnaire (mCDQ-24) in one of the studies.

The ARM-TD study was a phase 2/3 study evaluating the efficacy of deutetrabenazine compared to placebo in patients with TD.⁹ The deutetrabenazine dose was titrated over 6 weeks as needed to control symptoms up to a maximum dose of 48 mg per day divided twice daily (or up to 36 mg/day in patients on strong CYP2D6 inhibitors). At the end of the titration period the mean total daily dose was 38.8 mg. Deutetrabenazine decreased AIMS scores by -3.0 points compared to -1.6 points for placebo (MD -1.4; 95% CI, -2.6 to -0.2; $p=0.019$). A treatment difference of 5% is unlikely to be a clinically meaningful improvement in TD symptoms for patients. Treatment success as measured by the CGIC was 48.2% in the deutetrabenazine group compared to 40.4% in the placebo group (p -value not significant). PGIC treatment success was 42.9% in the deutetrabenazine group compared to 29.8% in the placebo group (p -value not significant). The difference in patient satisfaction, measured by the mCDQ-24, was not significantly different between deutetrabenazine and placebo, -11.1 and -8.3, respectively.

The AIM-TD study was a phase 3 study that evaluated 3 doses of deutetrabenazine (12, 24 and 36 mg/day) compared to placebo for the treatment of TD in adult patients (doses were divided twice daily).⁸ The mean change in AIMS score from baseline was -3.3 in the deutetrabenazine 36 mg group, -3.2 in the deutetrabenazine 24 mg group, -2.1 in the deutetrabenazine group and -1.4 in the placebo group at week 12. The proportion of the patients who achieved at least a 50% improvement in the AIMS score was 33% for deutetrabenazine 36 mg, 35% for deutetrabenazine 24 mg, 13% for deutetrabenazine 12 mg and 12% for placebo. The differences from placebo was 21% (NNT 5; $p=0.007$) for deutetrabenazine 36 mg and 23% (NNT 4; $p=0.005$) for deutetrabenazine 24 mg. CGIC treatment success occurred in 44% of deutetrabenazine 36 mg patients (ARR 18/NNT 6; $p=0.059$), 49% of deutetrabenazine 24 mg patients (ARR 23%/NNT 4; $p=0.014$), 28% deutetrabenazine 12 mg patients (not-significant compared to placebo) and 26% of placebo patients. PGIC treatment success rates were not statistically significantly different between deutetrabenazine and placebo for all comparisons.

The results of both studies of deutetrabenazine use in patients with TD were most applicable to patients with schizophrenia taking a DRBA with moderate TD symptoms. Risk of bias in both studies was low and they were considered fair quality. A 5% improvement in TD symptoms is unlikely to be meaningful to patients, as demonstrated by a lack of a clinically meaningful change in the patients’ perception of symptoms as measured by PGIC. Patients taking deutetrabenazine did not have a higher quality of life, as measured by mCDQ-24, compared to those taking placebo.⁸ The FDA sites twice a day dosing of deutetrabenazine as the only clear advantage of it over tetrabenazine. Small sample sizes and short duration of treatment for an indication which is often chronic prevents strong conclusions of efficacy.

Other studies that did not meet our inclusion criteria were the following: an indirect tolerability study between deutetrabenazine and tetrabenazine in patients with HD²³, a long-term safety study of deutetrabenazine in patients with severe TD²⁴ and an ongoing, open-label, single arm study of converting tetrabenazine to deutetrabenazine²⁵.

Clinical Safety:

The most common adverse events seen in more than 8% of patients randomized to deutetrabenazine and more than placebo were somnolence, diarrhea, dry mouth and fatigue. Severe adverse reactions occurred in 2.2% of patients in each group. Discontinuations due to adverse events occurred in one patient in each group. The risk of depression and suicidal ideation were similar in both groups. Deutetrabenazine carries a FDA Boxed Warning for its ability to increase the risk of depression and suicide in patients with HD and should be used cautiously in patients with a history of depression. In studies of deutetrabenazine there were no safety signals for worsening depression or suicidality; however, due to the small, short-term nature of approval studies the increased risk could not be ruled out.

The effect of deutetrabenazine on QT prolongation may be clinically relevant in patients who are poor CYP2D6 metabolizers or taking strong CYP2D6 inhibitors.²² Deutetrabenazine is closely related to tetrabenazine which has been shown to prolong the corrected QT interval by approximately 8 seconds. Metabolism of deutetrabenazine is primarily due to CYP2D6. Deutetrabenazine dosage reduction may be required if administered with strong CYP2D6 inhibitors.²¹

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:

- 1) Functional improvement
- 2) Symptom improvement
- 3) Health-related quality of life
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Total maximal chorea score change in HD
- 2) AIMS score change from baseline in TD

Table 4. Deutetrabenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Huntington Study Group ⁷ RCT, DB, DD, PC, PG, MC, Phase 3	1. DBZ* 2. PBO * Dose titrated over 8 weeks with a maintenance dose given for 4 weeks. Initiated at 6 mg/day and increased weekly by 6 mg/day till chorea was controlled, patient experienced adverse events or the maximum dose of 48 mg/day achieved. 12 weeks	Demographics: Mean Age: 54 y Male: 56% White: 83% Mean UHDRS functional capacity: 9.5 Mean UHDRS total maximal chorea score: 12.7 <u>Key Inclusion Criteria:</u> - HD verified by motor examination features and an expanded HTT CAG repeat sequence (≥36) - UHDRS total maximum chorea score of 8 or higher - UHDRS total functional capacity score of 5 or higher <u>Key Exclusion Criteria:</u> - Untreated psychiatric illness - prolonged QT interval, left bundle-branch block - hepatic or renal impairment - Use of antipsychotics,	<u>ITT:</u> DBZ: 45 PBO: 45 <u>PP:</u> DBZ: 44 PBO: 43 <u>Attrition:</u> DBZ: 2.3% PBO: 4.5%	Primary Endpoint: Total maximal chorea score change from baseline: DBZ: -4.4 PBO: -1.9 MD -2.5 (95% CI, -3.7 to -1.3) p<0.001 Secondary Endpoints: Treatment success determined by PGIC: DBZ: 23 (51%) PBO: 9 (20%) MD 31.1 (95% CI, 12.4 to – 49.8) P = 0.002 Treatment success determined by CGIC: DBZ: 19 (42%) PBO: 6 (13%) MD 28.9 (95% CI, 11.4 to – 46.4) P = 0.002 Patient satisfaction determined by mean SF-36: DBZ: 0.7 PBO: -3.6 MD: 4.3 (95% CI, 0.4 to 8.3) p = 0.03	NA 31%/4 29%/4 NA	Somnolence: DBZ: 5 (11.1%) PBO: 2 (4.4%) p-value NR Dry mouth: DBZ: 4 (8.9%) PBO: 3 (6.7%) p-value NR Diarrhea: DBZ: 4 (8.9%) PBO: 0 p-value NR Depression or agitated depression: DBZ: 2 (4.4%) PBO: 3 (6.7%) p-value NR D/C due to AE: DBZ: 1 (2%) PBO: 1 (2%) SAE: DBZ: 1 (2.2%) PBO: 1 (2.2%)	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (low) Computerized randomization algorithm via an interactive web-based randomization system randomized patients in a 1:1 ratio. Patients were stratified by prior exposure to tetrabenazine. <u>Performance Bias:</u> (low) Patients, site personnel, and study personnel were blinded to treatment. Adherence was accessed via pill count. Pills were identical in each group. <u>Detection Bias:</u> (unclear) Blinding of accessors was not described. <u>Attrition Bias:</u> (low) Attrition rates were low in both groups. Results were analyzed using ITT and LOCF for missing data. <u>Reporting Bias:</u> (low) Outcomes were reported as specified. Trial was funded by Auspex Pharmaceuticals. Applicability: <u>Patient:</u> Baseline functional scores suggest mild to moderate impairment. <u>Intervention:</u> Mean dose was 39.7 mg end of treatment period and 34.8 mg for patients with impaired CYP2D6 function (poor metabolizers or taking strong CYP2D6 inhibiting medications). The maximum deutetrabenazine dose is 48 mg/day suggesting study doses are appropriate. <u>Comparator:</u> Placebo comparison appropriate to establish efficacy where no standard of therapy exists. <u>Outcomes:</u> No minimal clinically important difference is available for total maximal chorea score but this a standardized measure for patients with HD, as well as the other secondary endpoints. <u>Setting:</u> Thirty-four sites in the United States and Canada.

		MAOIs, metoclopramide - Drugs known to prolong the QT interval						
2. Anderson, et al ⁹ (AIM-TD) MC, PG, PC, DB, Phase 3	1. DBZ 12 mg (D12)* 2. DBZ 24 mg (D24)* 3. DBZ 36 mg (D36)* 4. PBO 12 weeks *DBZ started at 12 mg/day divided twice daily and titrated by 6 mg/day till the randomized dose was achieved. Maintenance period was 8 weeks.	<u>Demographics:</u> Mean Age: 56 years Male: 45% TD duration: 5.6 y Baseline AIMS score (items 1-7): 8.4 <u>Key Inclusion Criteria:</u> - 18-80 years - ≥3 months of TD - AIMS score of ≥6 months - stable psychiatric illness - Use of antipsychotic for ≥30 days <u>Key Exclusion Criteria:</u> - Untreated psychiatric illness or neurological illness besides TD - Serious or unstable medical condition - Other treatment for TD - Hepatic or renal impairment	<u>mITT:</u> D12: 60 D24: 49 D36: 55 PBO: 58 <u>PP:</u> D12: 60 D24: 49 D36: 55 PBO: 58 <u>Attrition:</u> D12: 11% D24: 12% D36: 13% PBO: 9%	<u>Primary Endpoint:</u> LS Mean AIMS Change from Baseline: D12: -2.1 D24: -3.2 D36: -3.3 PBO: -1.4 D12 vs. PBO: MD -0.7 (95% CI, -1.84 to 0.42; p=0.217) D24 vs. PBO: MD -1.8 (95% CI, -3.0 to -0.63; p=0.003) D36 vs. PBO: MD -1.9 (95%; - 3.09 to -0.79; p=0.001) <u>Secondary Endpoints:</u> ≥ 50% AIMS Improvement: D12: 8 (13%) D24: 17 (35%) D36: 18 (33%) PBO: 7 (12%) D12 vs. PBO: NR D24 vs. PBO: OR 3.96 (95% CI, 1.46 to 10.72; p=0.005) D36 vs. PBO: OR 3.80 (95% CI, 1.40 to 10.36; p=0.007) CGIC Responders: D12: 17 (28%) D24: 24 (49%) D36: 24 (44%) PBO: 15 (26%) D12 vs. P: OR NR; p=0.734	NS NA NA 23%/5 24%/5 NS	<u>Somnolence:</u> D12: 0 (0%) D24: 1 (1.4%) D36: 3 (4.1%) PBO: 3 (4.1%) p-value NR <u>Headache:</u> D12: 5 (6.8%) D24: 2 (2.7%) D36: 5 (6.8%) PBO: 4 (5.6%) p-value NR <u>Diarrhea:</u> D12: 1 (1.4%) D24: 3 (4.1%) D36: 5 (6.8%) PBO: 2 (2.8%) p-value NR <u>SAEs:</u> D12: 2 (3%) D24: 6 (8%) D36: 4 (5%) PBO: 4 (6%) <u>D/C due to AES:</u> D12: 4 (5%) D24: 2 (3%) D36: 3 (4%) PBO: 2 (3%)	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (low) Patients randomized centrally 1:1:1:1 via interactive response technology. <u>Performance Bias:</u> (low) Patients, investigators and site personnel were masked to treatment assignment. <u>Detection Bias:</u> (low) Central raters that were blinded to treatment assignment assigned ratings. Full statistical analyses not reported. <u>Attrition Bias:</u> (low) Attrition was low and similar between groups. <u>Reporting Bias:</u> (low) Outcomes reported as pre-specified. Study was funded by manufacturer. Applicability: <u>Patient:</u> Sixty percent of patients had a schizophrenic diagnosis, 17% a bipolar diagnosis and 19% a depression diagnosis. Improvement in primary outcome was irrespective of DRBA; however, a greater improvement was seen in patients not taking DRBAs. <u>Intervention:</u> Doses of deutetrabenazine were consistent with other studies. <u>Comparator:</u> Placebo comparison appropriate. <u>Outcomes:</u> No minimal clinically important difference is available for AIMS score; however, AIMS score is a common surrogate endpoint used in TD studies. <u>Setting:</u> Seventy-five study sites in the US and Europe.

				D24 vs. PBO: OR 2.71 (95% CI, 1.21 to 6.05; p=0.014) D36 vs. PBO: OR 2.11 (95% CI, 0.96 to 4.65; p=0.059) PGIC Responders: D12: 14 (23%) D24: 22 (45%) D36: 22 (40%) PBO: 18 (31%) D12 vs. PBO: OR 0.69 (95% CI, 0.30 to 1.56; p=0.372) D24 vs. PBO: OR 1.82 (95% CI, 0.83 to 3.99; p=0.134) D36 vs. PBO: OR 1.51 (95% CI, 0.69 to 3.29; p=0.296)	23%/5 NS NS NS NS			
3. Fernandez, et al ⁸ (ARM-TD) MC, PG, PC, DB, Phase II/III	1. DBZ* 2. PBO 12 weeks *See Huntington Study Group for dosing	<u>Demographics:</u> Mean Age: 55 years Male: 56% TD duration: 6.2 years Baseline AIMS score: 9.6 <u>Key Inclusion Criteria:</u> - See Anderson, et al. <u>Key Exclusion Criteria:</u> See Anderson, et al.	<u>MITT:</u> DBA: 58 PBO: 59 <u>PP:</u> DBZ: 52 PBO: 52 <u>Attrition:</u> DBZ: 10% PBO: 12%	<u>Primary Endpoint:</u> LS Mean AIMS Change from Baseline: DBZ: -3.0 PBO: -1.6 MD -1.4 (95% CI, -2.6 to -0.2) p=0.019 <u>Secondary Endpoints:</u> CGIC Responder: DBZ: 48.2% PBO: 40.4% p- value reported as NS PGIC Responders: DBZ: 43% PBO: 30% p- value reported as NS Patient satisfaction as measured by mCDQ-24: DBZ: -11.1 PBO: -8.3 p- value reported as NS	NA NS NS	<u>Somnolence:</u> DBZ: 13.8% PBO: 10.2% p-value NR <u>Headache:</u> DBZ: 5.2% PBO: 10.2% p-value NR <u>Diarrhea:</u> DBZ: 5.2% PBO: 5.1% p-value NR <u>SAEs:</u> DBZ: 3 (5.2%) PBO: 5 (8.5%) p-value NR <u>D/C due to AEs:</u> DBZ: 1 (1.7%) PBO: 2 (3.4%) p-value NR	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias</u> (low) central randomization by an Interactive Technology Response System in a 1:1 ratio stratified by prior use of DRBA. <u>Performance Bias</u> : (low) Video assessment of TD was done by 2 investigators blinded to treatment assignment. <u>Detection Bias</u> : (low) Central raters that were blinded to treatment assignment assigned ratings. <u>Attrition Bias</u> : (low) Attrition was low for both groups and similar between deutetrabenazine and placebo. <u>Reporting Bias</u> : (low) Outcomes were reported as stated. The study was funded by the manufacturer. Applicability: <u>Patient</u> : 68% patients had a schizophrenia, 23% a bipolar disorder, and 26% a depression. The mean age older than most Medicaid patients. 80% patients also on DRBA. <u>Intervention</u> : See Anderson, et al <u>Comparator</u> : See Anderson, et al <u>Outcomes</u> : See Anderson, et al <u>Setting</u> : 46 sites in US and Europe.

Abbreviations: AE = adverse events; ARR = absolute risk reduction; CAG = cytosine-adenine-guanine; CI = confidence interval; CGIC = Clinical Global Impression of Change; DB = double-blind; DD = double-dummy; DBZ = deutetrabenazine; DRBA = dopamine receptor blocking agent; HADS = Hospital Anxiety and Depression Scale; HTT = huntingtin gene; ITT = intention to treat; LOCF = last observation carried forward; MAOI = monoamine oxidase inhibitors; mCDQ-24 = modified Craniocervical Dystonia Questionnaire; MD = mean difference; mITT = modified intention to treat; MOI = monoamine oxidase inhibitors; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PGIC = Patient Global Impression of Change; PP = per protocol; SAE = serious adverse events; TD = tardive dyskinesia; UHDRS = Unified Huntington's Disease Rating Scale; UPDRS = Unified Parkinson Disease Rating Scale.

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Appendix 1: Specific Drug Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INGREZZA safely and effectively. See full prescribing information for INGREZZA.

INGREZZA® (valbenazine) capsules, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia. (1)

DOSAGE AND ADMINISTRATION

- The initial dose is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- The recommended dose for patients with moderate or severe hepatic impairment is 40 mg once daily. (2.2)
- Consider dose reduction based on tolerability in known CYP2D6 poor metabolizers. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg and 80 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Somnolence: May impair patient's ability to drive or operate hazardous machinery. (5.1)
- QT Prolongation: May cause an increase in QT interval. Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. (5.2)

ADVERSE REACTIONS

Most common adverse reaction ($\geq 5\%$ and twice the rate of placebo): somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurocrine Biosciences, Inc. at 877-641-3461 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Dose adjustments due to drug interactions (2.3, 7):

Factors	Dose Adjustments for INGREZZA
Use of MAOIs with INGREZZA	Avoid concomitant use with MAOIs.
Use of strong CYP3A4 inducers with INGREZZA	Concomitant use is not recommended.
Use of strong CYP3A4 inhibitors with INGREZZA	Reduce dose to 40 mg.
Use of strong CYP2D6 inhibitors with INGREZZA	Consider dose reduction based on tolerability.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: No dosage adjustment is necessary for patients with mild to moderate renal impairment. Use is not recommended in patients with severe renal impairment. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUSTEDO safely and effectively. See full prescribing information for AUSTEDO.

AUSTEDO™ (deutetrabenazine) tablets, for oral use

Initial U.S. Approval: 2017

WARNING: DEPRESSION AND SUICIDALITY

See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO (5.2)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
- Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.2)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)
- AUSTEDO is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)

INDICATIONS AND USAGE

AUSTEDO is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

DOSAGE AND ADMINISTRATION

- The starting dose is 6 mg once daily. Titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum recommended daily dosage of 48 mg (24 mg twice daily) (2.1)
- Administer total daily dosages of 12 mg or above in two divided doses (2.1)
- Administer with food (2.1)
- Swallow tablets whole; do not chew, crush, or break (2.1)
- If switching patients from tetrabenazine, discontinue tetrabenazine and initiate AUSTEDO the following day. See full prescribing information for recommended conversion table (2.2)

- Maximum recommended dosage of AUSTEDO in poor CYP2D6 metabolizers is 36 mg per day (i.e., 18 mg twice daily) (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Tablets: 6 mg, 9 mg, and 12 mg (3)

CONTRAINDICATIONS

- Suicidal, or untreated/inadequately treated depression (4, 5.2)
- Hepatic impairment (4, 8.6, 12.3)
- Taking MAOIs, reserpine, or tetrabenazine (XENAZINE®) (4, 7.2, 7.3, 7.7)

WARNINGS AND PRECAUTIONS

- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.3, 7.4)
- Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs (5.4, 5.5)
- Sedation/somnolence: May impair the patient's ability to drive or operate complex machinery (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>8% of AUSTEDO-treated patients and greater than placebo) were: somnolence, diarrhea, dry mouth, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose of AUSTEDO is 36 mg per day (18 mg twice daily) (2.3, 7.1)
- Alcohol or other sedating drugs: May have additive sedation and somnolence (7.5)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to November Week 1 2017

Search Strategy:

#	Searches	Results
1	deutetrabenazine.mp.	12
2	valbenazine.mp.	18
3	tetrabenazine.mp. or Tetrabenazine/	1495
4	limit 3 to (english language and humans)	619
5	limit 4 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	41

Appendix 3: Proposed Prior Authorization Criteria

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Goal(s):

- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 2 months
- Renewal: Up to 12 months

Requires PA:

All VMAT2 inhibitors

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the treatment for an OHP-funded condition?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by OHP
3. Is the request for continuation of vesicular monoamine transporter 2 (VMAT2) inhibitor therapy previously approved by FFS criteria (patient has completed 2-month trial)?	Yes: Go to Renewal Criteria	No: Go to #4
4. Is the request for tetrabenazine or deutetrabenazine in a patient 18 and older with a diagnosis of chorea as a result of Huntington's disease?	Yes: Go to #5	No: Go to #7

Approval Criteria		
5. Does the patient have a baseline total maximal chorea score of 8 or higher?	Yes: Go to #6 Document baseline score: _____	No: Pass to RPh. Deny; medical appropriateness
6. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness
7. Is the request for deutetrabenazine in a patient 18 and older with a diagnosis of moderate to severe tardive dyskinesia?	Yes: Go to #8 Document baseline modified AIMS* score: _____	No: Go to #9
8. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	Yes: Go to #10	No: Pass to RPh. Deny; medical appropriateness
9. Is the request for valbenazine in a patient 18 and older with a diagnosis of moderate to severe tardive dyskinesia?	Yes: Go to #10 Document baseline modified AIMS* score: _____	No: Pass to RPh. Deny; medical appropriateness
10. Is there documentation that the patient has been diagnosed with Schizophrenia, Schizoaffective Disorder, or a Mood Disorder?	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness
11. Is the medication being prescribed by, or in consultation with, a neurologist or psychiatrist?	Yes: Go to #12	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria

12. Has the patient recently been evaluated and determined to not be at risk for a prolonged QT interval?	Yes: Approve for 2 months. Documented evidence of benefit required for renewal consideration (see renewal criteria).	No: Pass to RPh. Deny; medical appropriateness
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* The dyskinesia score for the modified Abnormal Involuntary Movement Scale (AIMS) for numbers 1-7

P&T/DUR Review: 11/2017

Implementation: TBD

Renewal Criteria

1. Is the request for a renewal of valbenazine or deutetrabenazine in a patient with tardive dyskinesia?	Yes: Go to #2	No: Go to #3
2. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement by a reduction in AIMS dyskinesia score (items 1-7) by at least 50%?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
3. Is the request for tetrabenazine or deutetrabenazine in a patient with chorea as a result of Huntington's disease?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement in total maximal chorea score of at least 2 points from baseline?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the mental status of the patient is stable and there is no indication of uncontrolled depression or risk of violent or suicidal behavior?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/2017 (KS)
Implementation: TBD